Progress in Implementing the Best Pharmaceuticals for Children Act (BPCA)

Leahey, Raju, Mattison

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Background

Over the years several practical problems discouraged the testing of drugs in children. These include difficulty conducting studies in children; ethical issues involving parental permission and the child's assent; needed technology to provide means to monitor patients and test very small amounts of blood; and the lack of incentives for pharmaceutical companies to study drugs in neonates, infants and children. Other difficulties have included the unforeseeable nature of some clinical responses in immature individuals; the possibility of unanticipated adverse reactions; the threat of effects on growth, development or health long after the drug's administration; difficulty in predicting dose-response or concentration-response relationships by extrapolation from data obtained in adults; ethical issues in clinical research involving children; and the lack of a suitable infrastructure for conduct of pediatric pharmacology research.

The NIH and the FDA recognized the need for improved knowledge in pediatric pharmacology. In 1994, in response to this need, the NICHD established a network of Pediatric Pharmacology Research Units (PPRUs). The PPRU Network conducts studies on the pharmacokinetics and pharmacodynamics of drugs in children and provides a locus for pre-and post-marketing clinical trials in children conducted by pediatric clinical pharmacologists in collaboration with the pharmaceutical industry and contract research organizations. Within this extensive network, pediatric subspecialty investigators work together with pediatric pharmacologists to carry out studies of drug therapy over a wide range of pediatric diseases. Studies in this Network provided the data needed and used by pharmaceutical companies to obtain pediatric labeling for a large number of drugs.

Also, in 1994, the FDA published a regulation (Pediatric Rule of 1994) that authorized the FDA to require the testing of a drug for pediatric use, if the course of the disease for which the drug is prescribed and the response to the drug are similar in adults and children. Pediatric labeling for these drugs must be based on extrapolation of efficacy in adults and on additional studies in children of pharmacokinetics, pharmacodynamics and drug safety. The 1994 rule was designed to improve pediatric labeling, but it did not substantially increase the number of well-designed, well-conducted pediatric drug trials for those drugs already on the market.

To further address the need for pediatric use information in drug labeling, Section 111 of the 1997 Food and Drug Administration Modernization Act (FDAMA) provided six months of additional marketing exclusivity to the manufacturers of certain drugs, if the manufacturer conducted pediatric clinical studies as specified in the Written Request (WR) issued by the FDA. Since the implementation of the pediatric provisions of FDAMA in 1997, 92 drugs have been granted exclusivity and approximately 63 drugs have new pediatric labeling.

Despite FDAMA, which provided new administrative tools and financial incentives to stimulate pediatric drug studies, the absence of a legal requirement that the manufacturer seek new pediatric labeling meant that a large number of off-patent drugs used daily in pediatric patients remained unstudied. This concern led to the development of the Best Pharmaceuticals for

Children Act of 2002 (BPCA), which in addition to renewing the provision for 6-months additional marketing exclusivity in return for pediatric testing of on-patent drugs, provides the mechanism for studying off-patent drugs.

The BPCA directs the Secretary of DHHS, acting through the Director of NIH, to establish a program for pediatric drug development. On October 25, 2002, the Director of NIH delegated to the Director of NICHD, the authority and responsibility for establishment and conduct of that pediatric drug development activity set forth under Part B, Title IV, Section 4091(a) and (b) of the Public Health Service Act (PHS Act). The activities within BPCA for drug development fall into three general categories: identification of those drugs needing study, written requests from the FDA to the manufacturers to conduct pediatric studies deemed necessary for those drugs by the FDA, and if manufacturers declined to do these studies, referral of the drug to NIH to conduct the necessary testing.

The intent of the BPCA is that the studies will provide necessary information for label modification of the drugs for use in pediatric populations. Upon receipt of delegation of authority for implementing the BPCA, the Director of the NICHD invited Directors of all relevant ICs to nominate a liaison to work with the NICHD to implement pediatric pharmacological drug research with therapeutic relevance to their IC. These liaisons have participated in activities conducted by NICHD and FDA staff relevant to the implementation of BPCA.

The Priority List of Off-Patent Drugs

The BPCA directs the Secretary of the DHHS, acting through the Director of the NIH and in consultation with the Commissioner of the FDA and experts in pediatrics and pediatric research, to develop and prioritize a list of "off-patent" drugs for which pediatric studies are needed. The initial list was published in a Federal Register of January 2003 and updated in August 2003. The 2004 drug prioritization list was posted in a Federal Register of February 2004. The drugs identified as highest priority for pediatric clinical trials, along with their indication for drug usage in pediatrics, and the current status of clinical testing, can be found at the end of this report in Tables 1 and 2.

The IC liaisons have participated actively in compiling the priority list of off-patent drugs called for in the BPCA. The NICHD in consultation with liaisons from other institutes and the FDA has developed and refined a prioritization process to select approximately15 candidate drugs on an annual basis for consideration for study from the list of approximately 180 off-patent drugs. As part of the selection process, the NICHD has established partnerships with pediatric drug study networks in other NIH Institutes to expedite the study of clinically important drugs with special relevance to the research programs of those Institutes, including the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Mental Health (NIMH).

In brief the process involves:

- Reviewing information describing frequency of use, availability of other drugs in the same therapeutic class, and public health benefit of the drug in question.
- Determining the availability of appropriate formulations for pediatric use. Pediatric use of drugs formulated for adults is one of the most frequent causes of medication errors in children.
- Reviewing published studies describing pharmacokinetics, efficacy and toxicity.
- Screening within each group and selecting high-priority drugs. Participants in screening include experts of all relevant NIH Institutes, opinion leaders of professional groups, experts in pediatric pharmacology, and pediatric medical specialty and subspecialty groups.

Clinical Trials For Off-Patent Drugs

Design of the clinical trials for pediatric populations has progressed based on collaborative efforts between the FDA and the NIH to develop written requests (WRs). The WR is the formal mechanism by which the FDA notifies manufacturers of the need to obtain additional clinical information about the drug for the selected indications and in specific populations. This process is described below.

The FDA first sends the WR to the manufacturers of the drug. If the manufacturers do not respond to the request to conduct the clinical trials described in the WR within 30 days, or decline to conduct the requested studies, the request is then referred to the NIH for development and conduct of the clinical trial.

Following referral of a WR, the NIH team led by a senior NICHD clinician-scientist reviews the literature. The NIH team, in collaboration with NICHD contracting staff, develops and publishes a request for proposal (RFP) that describes in detail the elements of the needed clinical trial. An ad hoc panel of experts convened by the NICHD Division of Scientific Review reviews submitted proposals. Negotiations with the best offerors are conducted, a selection is made, and a contract is awarded.

After the contract is awarded, the final protocol is derived under the guidance of the NICHD with input from the appropriate IC and by interaction with the Coordinating Center (CC), the Principal Investigator (PI), FDA and the various Institutional Review Boards (IRBs). The protocol then becomes the basis of the Investigational New Drug (IND) submission to the FDA.

During the clinical study the NICHD works closely with the Investigators, the Coordinating Center and the Data and Safety Monitoring Board to oversee the safety of the participants in the trial. When the clinical study is completed the data are submitted to the FDA for evaluation by its review staff and expert advisory panels with the intent of modifying the label to improve pediatric therapeutics. It is the intent of the NICHD to make data from these clinical trials available to interested investigators to improve information about design, conduct and evaluation of pediatric clinical trials.

It should be noted that not all drugs listed have had WRs developed. For instance, several drugs of interest to neonatologists on the list (Dopamine-Dobutamine, Furosemide-bumetanide) have the WR deferred because of clinical and scientific complexity in designing the clinical trials. These drugs will continue to be discussed by NIH scientists with input from FDA staff and outside experts to resolve these complexities before the clinical studies can be designed and implemented.

In FY 2003 the NICHD awarded a contract for the Data and Coordinating Center for the BPCA drug studies. In 2004, the NICHD has plans to award four contracts to conduct clinical trials for specific drug labeling. These include studies on Lorazepam (for status epilepticus and for sedation), Sodium Nitroprusside (for hypertension) and Baclofen (for spasticity). It is anticipated that the cost of each of these studies will be approximately $10 million and that they will vary from three to five years in duration. The status of these contracts is shown in Table 3 at the end of this report. Other contracts may be awarded depending on manufacturers responses to WRs.

Improving Knowledge About On-Patent Drugs

The BPCA also describes a process for improving knowledge concerning drugs that are on-patent when the needed studies will not be conducted by the drug manufacturer. The designated IC liaisons, along with NICHD staff, participate in the process of developing RFPs for pharmacological studies of drugs still on patent. Specifically, this involves drugs that are not being studied in pediatric populations despite the opportunity for additional six-months market exclusivity, but those that are being prescribed off-label for pediatric patients.

In accordance with the BPCA, an RFP is developed only after 1) the FDA has sent a WR describing a proposed pediatric trial to a pharmaceutical firm that manufactures the drug; 2) the manufacturer has denied or failed to respond to the WR within 120 days; and 3) the FDA has referred the drug to the Foundation for the National Institutes of Health (FNIH) and requested that it be considered for FNIH support of pediatric studies. FNIH will then work with pharmaceutical manufacturers to provide the needed funding to conduct the necessary pediatric clinical trials. Currently the FNIH has approximately $2 million available for the conduct of these needed pediatric studies in on-patent drugs. Table 4 at the end of this report includes the list of on-patent drugs and their indications that have been referred to the FNIH for consideration.

NICHD Program Management Activities

2003 Activities

Over the past two years since the initiation of the BPCA, NIH and FDA staff have conducted substantial work to implement this important legislation. The NICHD has developed

mechanisms to help plan conferences, workshops, and meetings and has contracted for program support to assist with developing a series of tracking systems for the WRs and for the list development process. Additionally, the NICHD is developing means to better communicate with the public and to facilitate outreach through use of a website, newsletters, and conference presentations.

Specific program management activities that were initiated by the NICHD during 2003 are highlighted below:

- The NICHD initiated briefing sessions with the FDA and the NIH Institute liaisons to discuss the processes and regulatory requirements for developing a WR, negotiating an IND, and preparing information for proposed label modification (July 2003).
- The NICHD awarded a five-year contract for the BPCA Coordinating Center to support the various clinical research activities (September 2003).
- The NICHD awarded a one-year purchase order to the University of Maryland School of Pharmacy for data describing the frequency of use of prescription drugs for children covered by Medicaid (September 2003).
- The NICHD initiated an Intra-Agency Agreement (IAA) with the National Institute of Environmental Health Sciences (NIEHS) to acquire literature reviews of drugs being considered for listing. The information collected was related to pediatric safety, efficacy, and pharmacokinetics (November 2003).
- Six WRs were issued by the FDA: Lindane/Scabies; Rifampin/infection; Baclofen/spasticity; Lithium/mania; Azithromycin/methicillin resistant staph endocarditis; Azithromycin/prevention of chlamydia infection; Morphine/pain. These WRs, refused by industry, are the basis for design of clinical trials by NICHD staff.
- The NICHD conducted a series of Colloquia for professional development and scientific consultation for the FDA and NIH staff participating in BPCA. Topics for presentation and discussion included: Clinical Trials in Pediatric Populations; Pediatric Pharmacoepidemiology – Measuring Frequency of Medication Use in Children; Dobutamine Usage in Neonates; Consent Issues in Pediatric Clinical Trials; and Efficacy vs. Safety: Study Design Issues.

2004 Activities

In addition to the awarding of contracts for specific drug labeling studies, the NICHD plans to award a series of contracts and IAAs in FY 2004 to provide state-of-the art literature review and meta-analysis to review current levels of information on drug use; drug efficacy; drug safety; appropriate dosing in pediatric populations; and formulations in pediatric populations.

Based on experience gained, the NICHD also initiated revisions to the listing procedures. The NICHD seeks to develop a yearlong process that will allow more extensive contact with stakeholders and improved outreach to professional organizations, to increase their input. Towards this aim:

- The NICHD has scheduled the next bi-annual meetings with the NIH Institutes involved to discuss progress to date with BPCA-related activities.

- The NICHD and the FDA are planning a Neonatal Drug Initiative (NDI) workshop in Baltimore, MD during the spring of 2004. This is the first of a proposed series of working meetings to explore approaches for the design and conduct of clinical trials to enhance the development of safe and effective drug therapies in neonates and pre-term infants. The focus of this initial working meeting will be to discuss the current status of therapeutic pharmaceutical research in neonates and preterm infants. The meeting will focus on identifying gaps in existing knowledge in this field and strategies to improve therapy for cardiovascular, neurological and pulmonary conditions and treatment of pain in newborns.
- The NICHD is planning a public meeting in the fall of 2004 to gather additional input from Government partners, academia, parents and pediatric research advocacy groups and industry on the list prioritization process.

Conclusion

Over the past two years since the initiation of BPCA there has been substantial work conducted by NIH and FDA staff with the leadership of the NICHD to implement this important legislation. The two organizations have established a very congenial and productive relationship that provides the infrastructure for BPCA. Within the NIH, the NICHD has similarly worked to develop and support a collaborative environment between Institutes and Centers to engage relevant colleagues in the identification of drugs of highest priority for study in pediatric populations and the design of clinical trials.

Drug development, especially for children, requires a thoughtful and strategic approach. It is necessary to understand which drugs are being used to treat children who are in the hospital as well as the drugs used to treat children who are outpatients. At the present time, there are a very small number of drugs that were developed specifically to treat children (e.g., Surfactant, Nitric oxide). Most pediatric pharmacologic therapeutics have been adapted from drugs used in adults. The development process for many of these adult drugs typically spanned a decade.

Over the past two years, the NIH has established (and is improving) mechanisms to identify drugs frequently used in children as well as the conditions for which they are used, and prioritize the need for further study of them. This information allows us to identify those drugs most urgently needing clinical study in children. The NIH has also developed the description for, identified through a competitive process, and awarded a clinical coordinating center to carry out this activity under NIH guidance.

Once a drug enters clinical trials in humans, it typically takes approximately five years for the trials to be completed and the FDA review finalized. As a result of the time needed to conduct these trials, much of the work initiated under the BPCA is still in progress.

Table 1: List of Off-Patent Priority Drugs – 2003

Drugs needing pediatric study	Indications for pediatric use	Status
Lorazepam	Sedation in the Intensive Care Unit	1
	Treatment of status epilepticus	1
Nitroprusside	Hypertension, blood loss prevention	1
Baclofen	Oral treatment of spasticity, most commonly from cerebral palsy	1
Azithromycin	Prevention of Bronchopulmonary dysplasia/ureaplasma pneumonia	1
	Prevention of Chlamydia pneumonia/conjunctivitis in neonates	2
Lithium	Treatment of mania in bipolar disorder	1
Ampicillin/sulbactam	Pediatric infections	2
Diazoxide	Hypertension	2
	Hypoglycemia	2
Isoflurane	Induction and maintenance of general anesthesia	2
Meropenem	Pediatric infections	2
Metoclopramide	Gastroesophageal reflux	2
Piperacillin/tazobactam	Pediatric infections	2
Promethazine	Nausea/vomiting	2
Rifampin	Methicillin resistant staph aureus infection producing endocarditis	2
	Central nervous system (CNS) shunt infections	2
Lindane	Second-line treatment of scabies	2

Heparin	Maintenance of catheter patency	Drug already labeled for children
Bumetanide	Diuresis	3
Furosemide	Diuresis	3
Dobutamine	Hypotension, low cardiac output in infants	3
Spironolactone	Diuresis	3

Status: 1=RFP developed; 2=Written Request being developed by the FDA in consultation with the NIH; 3=Drug undergoing extensive review by NIH and FDA

Table 2: List of Priority Off-Patent Drugs – 2004

Drug needing pediatric study	**Indications for pediatric use**
Ampicillin	Infections
Ketamine	Sedation
Vincristine	Malignancies
Dactinomycin	Malignancies
Metolazone	Diuresis

Table 3: Status of Off-Patent Drug Study Contracts

Drug needing pediatric study	**Indications for pediatric use**	**RFP Status**
Lorazepam	Status epilepticus	Award pending
Lorazepam	Sedation	Entering negotiations
Sodium Nitroprusside	Control of blood pressure	Entering negotiations
Baclofen	Spasticity cerebral palsy	RFP being developed

Table 4: On-Patent Drugs Referred to the Foundation for The National Institutes of Health

Drug	Indications
Morphine	Pain
Bupropion	Depression and smoking cessation
Sevelamer	Hyperphosphatemia in chronic renal insufficiency
Zonisamide	Partial seizures